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14. ABSTRACT
We proposed to investigate the role of our newly designed PET imaging probe (FMDHT) in the early detection of ovarian cancer using PET. Our probe is specifically designed to target androgen receptors. Since ovarian cancers also express these receptors, we anticipated that FMDHT may be able to detect these receptors at an early stage when the tumor isles aggressive and possibly managed easier. To accomplish that, we proposed and performed assessment of FMDHT accumulation in ovarian cancer xenografts (OVCAR) using female mice. Although, FMDHT accumulated in these tumors, the receptor concentration was low in these tumors, thus eluding the copious accumulation of this probe. In addition, we assessed the accumulation of FMDHT in female monkeys, especially in the ovaries. Our initial hypothesis was that since the androgen receptor concentration is low in normal ovaries, FMDHT would accumulate sparingly in normal ovaries of non-human primates. We then hypothesize that the androgen receptor concentration would increase (much higher) during the malignancy, we would observe and increased probe signal in presence of ovarian cancer. As expected, PFDHT accumulation in the ovaries was low and could not differentiate normal ovaries from other normal tissues. This was an important and encouraging property of this imaging probe. In near future, we would like to extend this observation to cancer model in large animal species to assess the ability of FMDHT in detecting androgen receptor positive ovarian cancer.

15. SUBJECT TERMS
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REPORT:

Introduction:

Although, androgen receptors (AR) are mainly implied in prostate cancer, they an play important role in the pathogenesis of ovarian cancer (1). AR are expressed in 70-90% of ovarian cancer tissues. A high risk of ovarian cancer is implicated in post menopausal women exhibiting high androgen serum levels (2) suggesting a diagnostic and perhaps therapeutic role of androgen mediated intervention. NIH:OVCAR-3 cell line has been established from malignant ascites of a patient with adenocarcinoma of the ovaries (3). This cell line show copious presence of androgen receptors (3). Most often ovarian cancer is detected during women's routine gynecological examination. If detectable abnormalities are found during the palpitation of ovaries, ultra-sound, X-ray and other diagnostic tests are prescribed. Ovarian cancer is also known as 'a silent killer', because more often no symptoms are noted until the disease has progressed to an advanced stage. Early detection of ovarian cancer leads to a cure rate exceeding 90%. Unfortunately, no diagnostic tests are available to ensure high cure. Although, PET imaging technology is outstanding, lack of a suitable probe has increased the risk of missing ovarian cancer detection in large number of female patients. We propose to develop a probe that is highly specific for this application. Our laboratory has been involved in the development of various radiolabeled sex-steroids as diagnostic agents. Recently, our laboratory developed an F-18 labeled androgen *i.e.* 7α-[^{18}F]-17α-CH_3-5α-DHT (FMDHT) to aid in detection of androgen responsive prostate cancer and reported its avid accumulation in androgen receptors. Since AR is expressed copiously in ovarian cancer, FMDHT would be an excellent probe. We hypothesize that AR would be an excellent biomarker for the detection of ovarian cancer and its metastasis. We have already identified and tested this probe in other tumor model. In this proposal, we wanted to assess FMDHT characteristics in modles of ovarian cancer.

Body:

We proposed to assess the potential of our PET imaging probe FMDHT in early detection of ovarian cancer. To accomplish our aims, we proposed three main takss. Herein, we report findings from each task.

Under Task 1 and 2, we incorporated radiochemical synthesis and biodistribution studies. Task 3 was dedicated to PET imaging studies using non-human primatesHerein, we outline results obtained from the proposed studies.

1. We synthesized F-18 FMDHT in 14±5% radiochemical yields using our automated radiochemical synthesis module and microwave heating procedure.
2. Initially, we performed biodistribution studies using FMDHT in female athymic mice as proposed. The results from these biodistribution studies are tabulated below. A low uptake in normal tissue was s imilar tot hat observed earlier for the male mice (data not shown). A low F-18 uptake in the bones reflected metabolic stability of this compound in vivo. Liver and kidneys show appreciable accumulation of F-18 indicating its excretion pathway similar to that for other steroidal molecules.

%ID/g tissue at 60 min

Tissues	Mean	SD
Liver	5.756	1.087
Spleen	0.469	0.065
Lung	0.606	0.085
Heart	0.764	0.247
Kidneys	1.692	0.177
Sm Int.	1.246	0.745
Muscle	0.490	0.141
Bone	0.894	0.232
Blood	0.887	0.257
Brain	0.170	0.082
Fat	0.462	0.169

3. Subsequently, we performed biodistribution studies in female athymic mice bearing OVCAR tumor xenograft, as proposed. The results from these biodistribution studies are tabulated below. The F-18 uptake in the tumor was slightly lower than that observed for other androgen responsive tumors, especially the prostate specific (LnCAP) tumor.

	%ID/g tissue at 60 min	
Tissues	**Mean**	**SD**
Liver	5.681	1.303
Spleen	0.550	0.203
Lung	0.738	0.336
Heart	0.930	0.431
Kidneys	1.465	0.313
Sm Int.	3.406	3.642
Muscle	0.537	0.245
Bone	0.862	0.301
Blood	0.944	0.297
Brain	0.275	0.236
Fat	0.759	0.390
Tumor	0.704	0.227

4. The tumor to normal tissue ratio was quite low in these female mice. To assess imaging capabilities of FMDHT to detect OVCAr tumor in vivo, we performed microPET studies. Tumor was not visible on microPET scans, perhaps owing to low androgen receptor density in these tumors. It is also likely that OVCAR tumor xenograft may not be ideally suited for such studies. These studies suggest that further evaluation of FMDHT to detect ovarian cancer is warranted, perhaps requiring use of more appropriate tumor xenograft/host combination.
5. Under task 3, we performed whole body imaging in non-human primates using FMDHT. The distribution characteristics of FMDHT in female cynamolgus monkeys were quite favorable. As hypothesized, the ovaries were not distinguishable from other surrounding tissues. Nonetheless, no other androgen positive tissues could be identified in PET scans performed using these normal monkeys.

Key Research accomplishments:

1. We further optimized the radiochemical synthesis of FMDHT and automated its synthesis to reduce radiation exposure to synthetic chemists.
2. This is a first study assessing the biodistribution characteristics of FMDHT in ovarian cancer model.
3. Non-human primate studies show a very retention of FMDHT in vivo indicating good imaging characteristics of this compound.
4. Based on its accumulation properties in androgen positive tumors and low uptake in normal tissues as seen from biodistribution and PET imaging studies, FMDHT is a good candidate to image androgen receptors in vivo.

Reportable outcomes:

1. We plan to submit two abstracts from these studies.
2. We plan to submit a manuscript describing biodistribution study results acquired using normal mice and mice bearing OVCAR tumor xenograft.
3. More PET imaging studies are necessary to compile imaging results.

Conclusion: FMDHT is a good PET probe to identify tissues with androgen receptors, especially the tumors rich in these receptors. Low uptake in normal tissues and modest uptake in tumor was seen using mice bearing OVCAR tumor xenograft. Normal ovaries were not identifiable on PET scans, suggesting low concentration of androgen receptors in ovaries, below the limit of detection in this setting.